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Award Number: W81XWH-04-1-0275

TITLE: Antioxidant Prophylaxis in the Prevention of Prostatic Epithelial Neoplasia

PRINCIPAL INVESTIGATOR: A. Pratap Kumar, Ph.D.
Rita Ghosh
Nicole Arevalo
Lori Gardner

CONTRACTING ORGANIZATION: AMC Cancer Research Center
Denver, Colorado 80214-1897

REPORT DATE: February 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	February 2005	Annual (1 Feb 04 - 31 Jan 05)

4. TITLE AND SUBTITLE
Antioxidant Prophylaxis in the Prevention of Prostatic Epithelial Neoplasia

5. FUNDING NUMBERS
W81XWH-04-1-0275

6. AUTHOR(S)
A. Pratap Kumar, Ph.D.
Rita Ghosh
Nicole Arevalo
Lori Gardner

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
AMC Cancer Research Center
Denver, Colorado 80214-1897

E-Mail: kumarp@amc.org

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

This first Year I annual report describes the research accomplishments primarily associated with Task I as outlined in the approved statement of work. As per this, we have started experiments feeding antioxidant supplemented diet (different doses) that are currently ongoing. We will be terminating the experiments by the end of May 2005 (just about 15 months after staring the project) which is within the time-frame of completing Task 1. Since this work is ongoing we have no major findings to present at this time. In year II (March 2005-February 2006) we will continue making progress towards accomplishing the tasks as proposed in the original grant application including analysis of tissues for PIN formation and its response to intervention with antioxidant supplemented diet through histopathological examination; determine the levels of T and E2 in the serum, AR protein in the tumors to correlate with the observed histological changes.

14. SUBJECT TERMS
Oxidative Stress; Prostatic Intraepithelial Neoplasia (PIN); Antioxidants and Prevention

15. NUMBER OF PAGES
5

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Introduction:

Although prostate cancer is considered to be a disease of older men, a significant number of relatively young men exhibit the earliest signs of prostate cancer. This suggests that the disease is initiated early and remains latent until some factors trigger it to become malignant. This long latency of prostate cancer progression provides an opportunity for intervention to prevent the initial disease from becoming cancerous. Since treatment options for prostate cancer are very limited for initial stages of the disease and unavailable for metastatic disease, it is imperative that other means to control the disease be vigorously tested to reduce the number of prostate cancer-related deaths in the United States.

Oxidants produced as by-products of cellular metabolism have been implicated in the genesis of prostate cancer. Oxidative stress is caused by an imbalance of cellular endogenous oxidant and antioxidant levels. Laboratory studies using different model systems indicate that oxidative stress markers increase and antioxidant enzyme levels decrease during prostate cancer progression. Oxidative stress generated by dietary fat and androgens has been implicated in prostate cancer. Further epidemiological studies with a variety of antioxidants such as selenium, tocopherols, lycopene, β-carotene etc. have been found to be effective in lowering prostate cancer risk. Although these data suggest the importance of oxidative stress and antioxidants in prostate cancer, they are flawed in that they do not add to our understanding of the nature and amounts of antioxidants that are beneficial. This is extremely important since several classes of oxidants are produced and

a single antioxidant cannot quench all the different species of oxidants produced from cellular metabolism. Further, time is an extremely important factor for successful antioxidant prophylaxis. Taken together, the stage of prostate development and the kinds of antioxidants used would play a major role in determining the success of antioxidant prophylaxis. This proposal is a first step in beginning to understand whether antioxidants can prevent or delay the formation of PIN. Based on evidence presented in the literature, ***we hypothesize that a combination of antioxidants can prevent or delay the development of Prostatic Intraepithelial Neoplasia in a T/E_2 model of PCA by modulating the level of oxidative stress markers and endogenous antioxidant levels.*** To test our hypothesis we propose three specific aims.

1) Determine the ability of antioxidants to prevent or delay the development of Prostatic Intraepithelial Neoplasia (PIN) and relate it to changes in T/E_2 in the serum and AR.
2) Determine the levels of oxidative stress markers of DNA, protein and lipids following antioxidant supplementation.
3) Determine the levels and functional ability of endogenous antioxidant components following antioxidant supplementation.

There has been no change in the specific aims proposed.

Key Research Accomplishments:

We focused solely on accomplishing task 1 in Year I (March 1 2004 through January 2005) as proposed in the grant application:

Task 1: Determine the ability of antioxidants to prevent or delay the development of Prostatic Intraepithelial Neoplasia (PIN) (**months 1-18**). This involves (a) breed Noble rats; (b) start antioxidant supplementation; (c) initiate PIN formation with hormone treatment; (d) terminate feeding protocol for 16 and 32 weeks.

There was minor delay in initiating the project due to difficulties associated with personnel hiring. We have obtained enough Nobel rats and started feeding them with the antioxidant supplemented diet (please see table 2 of original grant application for composition and level) and induced with hormones. We will be terminating the experiment by the end of May 2005 (just about 15 months after staring the project) which is within the time-frame of completing Task 1.

In year II (March 2005-February 2006) we will continue making progress towards accomplishing the tasks as proposed in the original grant application. In aim 1, we will analyze the tissues for PIN formation and its response to intervention with antioxidant supplemented diet through histopathological examination; determine the levels of T and E2 in the serum, AR protein in the tumors to correlate with the observed histological changes. In aim 2, we will measure oxidative stress markers of DNA, proteins and lipids such as 8-oxo-dG, protein carbonyl content and lipid peroxidation products respectively will be assayed in the prostate tissue and serum obtained from control animals (with and without hormone stimulation) and animals on antioxidant supplemented diet.

Reportable outcomes: None at this time.

Conclusions:

We anticipate obtaining data from Task 1, finishing analysis and being able to publish results by the end of year. During second year of grant period we anticipate demonstrating whether or not antioxidant prophylaxis can be used to prevent PIN formation. This will have a major impact in reducing prostate cancer incidence and mortality since it would nip the disease in the bud. We also expect to see a correlation between a particular oxidative stress marker and PIN inhibition it can be developed as a marker for predicting the disease risk

during this grant period. Since prostate cancer progresses asymptomatically and slowly knowing the kinds and amounts of antioxidants and the stage of disease progression (pre or post neoplastic) when antioxidants offer the maximum protection could lead to a decrease in incidence or delay the development of clinically evident cancer.